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(19)(CA) APPLICATION FOR CANADIAN PATENT (12)

(54) Procaterol Microspheres Controlled-Release Aerosol

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Canada

ABSTRACT

The present invention relates to a method of making a composition for delivery by aerosol inhalation comprising dispersion of albumin microspheres in a propellant, that provides controlled-release delivery of pharmaceutically active agents, particularly bronchodilating agents such as procaterol or procaterol hydrochloride; the composition for use in the delivery; its use and a device for this use.

PROCATEROL MICROSPHERES CONTROLLED-RELEASE AEROSOL

FIELD OF INVENTION

The present invention relates to a method of making a composition for delivery by aerosol inhalation comprising albumin microspheres, preferably in a propellant, that provides controlled-release delivery of pharmaceutically active agents, particularly bronchodilating agents such as procaterol or procaterol hydrochloride; the composition for use in the delivery; its use and a device for this use.

BACKGROUND OF INVENTION

International application published under the Patent Cooperation Treaty (PCT) publication number WO 87/05803 describes pharmaceutical compositions for administration of β_2-receptor active substances including procaterol by inhalation and comprising liposomes. The description provides for aerosolizing a composition of a selected quantity of lipid-based solid material which is said to spontaneously form or reconstitute liposomes in an aqueous milieu. The present invention differs from the described composition as the invention does not provide a lipid-based material for aerosolizing and further does not provide for delivery by the formation of liposomes. The composition also differs from the present invention by the controlled-release property of the present invention.

International application published under the PCT publication number WO 87/05213 also describes preparation of pharmaceutical compositions for

inhalation containing microgranules of solid water-soluble diluents and a lubricant. Although the compositions may include procaterol, the other components are different from the present invention. For example, WO 87/05213 teaches the preparation of an excipient called a conglomerate in the form of microgranules of a solid water-soluble vehicle such as lactose, xylitol, arabinose, dextran, mannitol or the like with a suitable lubricant such as sodium benzoate, magnesium stearate, colloidal silica, hydrogenated oils, fatty bases, etc.

In contrast, the present invention prov.des controlled release of a pharmaceutically active agent, preferably procaterol or procaterol hydrochloride in a water insoluble matrix.

U.S. Patent No. 4,696,938 describes insecticidal aerosol compositions. Although many of the components of this composition are the same as or similar to those employed in the present invention, various components acceptable in an insecticidal application are included which are not suitable for pharmaceutical use. No details of the preparation of an aerosol composition are described. The Example for an aerosol in the disclosure of the patent indicates the components, a toxicant and toxicant impurities and Freon 12, are mixed and packaged under pressure in a suitable container equipped with a release spray valve. This teaching is not suitable for the present controlled-release aerosol for procaterol.

S.R. Walker et al., "The Clinical Pharmacology of Oral and Inhaled Salbutamol", Clinical Pharmacology and Therapeutics, Vol.13, No. 6, p.861 (1972) describes the pharmacology of inhaled salbutamol which is a selective β_2-receptor stimulant, i.e., an effective bronchodilator. However, no description shows preparation of an aerosol and therefore differs from the present invention for controlled-release of procaterol.

Various references describe albumin for delivery of drugs in parenteral applications, particularly for

cancer treatment. These include, CRC Critical Reviews in Therapeutic Drug Carrier Systems, Yasunori Morimoto and Shigeru Fujimoto, "Albumin Microspheres as Drug Carriers," Volume 2, Issue 1, pp.19-63; Microspheres and Drug Therapy. Pharmaceutical, Immunological and Medical Aspects, edited by S. S. Davis, L. Illum, J. G. McVie and E. Tomlinson (1984), Elsevier Science Publishers B. V., Chapter 1 "Human serum albumin microspheres for intraarterial drug targeting of cytostatic compounds. Pharmaceutical aspects and release characteristics," pp.75-89 by E. Tomlinson et al., Chapter 4 "Development and testing of proteinaceous nanoparticles containing cytotoxics," pp.117-128 by R. C. Oppenheim et al., Chapter 3 "Adriamycin-loaded albumin microspheres: Lung entrapment and fate in the rat," pp.205-215 by N. Willmott et al., Chapter 9 "Drug entrapment within native albumin beads," pp.295-307 by T.D. Sokoloski and G.P. Royer, and Chapter 10 "Hydrophilic albumin and dextran ion-exchange microspheres for localized chemotherapy," pp.309-325 by E.P. Goldberg et al.; Biomedical Applications of Microencapsulation, Editor: Franklin Lim, CRC Press Inc., Boca Raton, Florida (1983), Chapter 3 "Biodegradable Microspheres for Parenteral Administration," pp.53-75 at 66 by C. Thies and M. Bissery; E. Tomlinson and J. G. McVie, "New directions in Cancer Chemotherapy 2. Targeting with Microspheres," Pharmacy International, November, 1983, pp. 281-284; and N. Willmott and P. J. Harrison, "Characterization of freeze-dried albumin microspheres containing the anti-cancer drug adriamycin," International Journal of Pharmaceutics, 43 (1988) 161-166.

Extended-Release Dosage Forms by Leszek Krowczynski translator Dorota Porebska Brozyna, CRC Press, Inc., Boca Raton, Florida, pp. 71-72 describes an aqueous suspension (0.5 ml) of human serum albumin and staphylococcal protein A mixed with cottonseed oil (60

ml) and homogenization of the emulsion by sonification for 1 min. at 60°C followed by denaturation at 120 to 125°C for 10 min. Use of egg albumin is also mentioned by Krowczynski. The resultant microspheres were air dried for parenteral administration. Although these microspheres comprise a pharmacological component the reference teaches intraarticular injection of the microspheres which is different from an aerosol delivery of a pharmacologically active component. Thus, the article does not provide microspheres for extended-release delivery of procaterol in an aerosol as set out in the present invention.

SUMMARY OF INVENTION

The present invention provides a controlled-release pharmaceutical formulation for use in an inhalation aerosol comprising a pharmaceutically active agent, preferably procatero., and albumin in the form of microspheres.

The present invention provides a novel method for preparing a composition for controlled-release delivery of a pharmaceutically active agent by inhalation aerosol which comprises dispersing microspheres, wherein the microspheres are a controlled-release formulation comprising a pharmaceutically active agent and albumin; in an aerosol-type propellant.

The present invention also provides a composition for controlled-release delivery of a pharmaceutically active agent by inhalation aerosol which comprises a dispersion of microspheres, wherein the microspheres are a controlled-release pharmaceutical formulation of a pharmaceutically active agent and albumin; in an aerosol-type propellant.

The present invention is also a method of treating a disease condition which comprises administering microspheres by inhalation aerosol, wherein the

microspheres are a controlled-release formulation comprising a pharmaceutically active agent effective for treating the disease or condition and albumin; by metered-dose.

Finally, the present invention is an inhalation device for delivery by inhalation aerosol. The inhalation device may be a powder-inhalator such as Spinhaler®, Rotahaler®, Turbuhaler®, etc. or a pressurized dose-aerosol. The powder-inhalator provides a selected quantity of microspheres in a form suitable for inhalation. The microspheres are a controlled-release formulation comprising a pharmaceutically active agent together with albumin. No powder-inhalers containing a controlled-release formulation exist on the market.

The pressurized dose-aerosol is a pressure-tight container having a valve-controlled opening, optionally equipped with a metered dose device, and containing a self-propelling composition capable of providing microspheres in aerosol form. The self-propelling composition comprises a pharmaceutically acceptable propellant in which the microspheres are dispersed. The microspheres are a controlled-release pharmaceutical formulation preferably comprising a pharmaceutically active agent together with albumin. On operating the metering valve of the aerosol container, the microspheres are dispensed in a stream of propellant. No pressurized dose-aerosols containing controlled-release microspheres exist on the market. However, controlled-release microspheres having pharmaceutically active agents together with albumin are present in various other suspending agents particularly suitable for parenteral use.

The pharmaceutically active agents of the present invention are compounds appropriate for delivery by inhalation aerosol, preferably such agents having high potency. More preferably the agent is a bronchodilating

agent and most preferably is procaterol or procaterol hydrochloride.

Stabilizing agents may be present on each of the above described microspheres having a pharmaceutically active agent and albumin.

DETAILED DESCRIPTION OF INVENTION

Pharmaceutically active agents for inhalation aerosol which may be incorporated into the microspheres of the present invention are 5-lipoxygenase or cyclooxygenase inhibitors and antiallergy agents generally; antiinflammatory agents; and particularly bronchodilating agents. For example, isoproterenol hydrochloride, isoetharine hydrochloride, metaproterenol, albuterol, terbutaline, cromolyn atropine sulfate, and preferably procaterol hydrochloride may be used.

The albumin microspheres suitable for use in the inhalation aerosol of the present invention microencapsulate the active agent which may be prepared either by thermal denaturation at elevated temperatures, 80° to 140°C for from 2 to 60 min., or chemical cross-linking in vegetable oil or isooctane solution. For example, an aqueous solution or suspension of the active agent, ? to 200 mg/ml, and serum albumin, 18 to 1800 mg/ml, is mixed with an oil, 10 to 1000 ml, preferably vegetable oil, and an emulsion prepared by sonification for 0.5 to 3 min. The emulsion is added to an additional 50-50,000 ml oil and heated for 0.5 to 60 min. at 80° to 140°C. The resultant microspheres are washed with n-hexane and separated by centrifugation.

Procaterol hydrochloride may not be sufficiently stable to resist elevated temperatures used for albumin denaturation. Thus, it is suggested a stabilizer may be added, either in the oil or aqueous phase or both oil and aqueous phases in the above description.

Specifically, for example, in a procaterol hydrochloride concentration of 20 ng/ml in water, the procaterol is decomposed ca. 5% in 100 minutes at 98°C. With the addition of ascorbic acid (0.05%) as a stabilizer in the aqueous phase, no decomposition occurs. One of ordinary skill would recognize use of other stabilizers may include sodium metabisulfite, sodium sulfite, sodium bisulfite, isoascorbic acid, sodium isoascorbate, ascorbyl palmitate, ethyl gallate, propyl gallate, gallic acid, cysteine hydrochloride, thioglycollic acid, thiosorbitol, sodium thiosulphate, tocopherols, butylated hydroxytoluene, butylated hydroxyanisole, t-butylhydroquinone and the like.

The microspheres may be stored in hexane or washed with a propellant for dispersion in the propellant. The microspheres and compressed air or microspheres and propellant in a dispersion composition is filled into a device for inhalation aerosols and appropriately charged to an appropriate air pressure or with additional propellant to an appropriate pressure. This microsphere containing a pharmaceutically acceptable agent microencapsulated in albumin is ready for compressed air delivery inhalation use or metered-dose inhalation use.

The oils for forming the emulsion include edible animal and vegetable oils such as various fish oils, soybean, safflower, sunflower, corn, cottonseed, rapeseed, sesame, and bran oils, preferably cottonseed oil.

The serum albumin suitable for use in the microspheres include human, egg, or other animal such as rabbit or bovine, preferably human or bovine serum albumin.

The propellants that may be used in the present invention are either compressed air or pharmaceutically acceptable propellants for metered-dose inhalants such as various chlorofluorocarbons, fluorocarbons or

hydrocarbons which generate a positive pressure within a sealed container.

The oil phase will typically contain emulsifiers, preferable emulsifiers having a low HLB (Hydrophile-Lipophile Balance). Examples of such emulsifiers include glyceryl monostearate, glyceryl monoleate, sucrose distearate, sorbitan monostearate, sorbitan, monopalmitate, sorbitan monolaurate, and sorbitan esters marketed under the trade name Span.

The preferred microspheres of the present invention microencapsulate a potent bronchodilator in albumin.

The most preferred microspheres of the present invention microencapsulate the potent bronchodilator, procaterol hydrochloride.

The release profile can be controlled depending on the amount of albumin that is used for microencapsulation.

The encapsulation process is preferably optimized to prepare microspheres in the particle size range of 1 to 10 μm(microns) and preferably in the range of 1 to 3 microns. The overall ratio of active agent to albumin is typically from 1 to 10. A relatively large amount of albumin, i.e., up to 20 milligrams, can be used to encapsulate the most preferred active agent, procaterol hydrochloride.

P. E. Morrow in Chapter 21 of Airway Dynamics entitled, "Dynamics of Dust Removal From The Lower Airways: Measurements and Interpretations Based upon Radioactive Aerosols," describes size-deposition relationships for dust deposition and removal for a dust cloud or aerosol. This article teaches that dust or aerosol of size ranges, for example from 1 to 10 microns, preferably 1 to 3 microns, such as the microspheres which are the present invention, could stay in the lung for an extended period of time. That is, in the light of this teaching, the microspheres of the

present invention would provide a controlled release of a pharmaceutically active agent by aerosol inhalation.

Generally, an ordinarily skilled physician will readily determine and prescribe an effective amount of the inhalation aerosol having the microspheres for prophylactic or therapeutic treatment of the condition for which such treatment is administered.

The composition described below is a dispersion of microspheres containing procaterol hydrochloride microencapsulated in serum albumin which microspheres are dispersed in a propellant having the trade name Freon 11 and/or Freon 12.

EXAMPLE 1

Preparation of Albumin Microspheres

An aqueous solution (1 ml) containing 20 mg of procaterol hydrochloride and 180 ml of bovine serum albumin is mixed with cottonseed oil (100ml) and the emuision is prepared by sonication for 1.5 minutes at 50°C. This water/oil emulsion is added to 200 ml of constantly stirred cottonseed oil at 110°C for 30 minutes. The resultant microspheres are washed with n-hexane and separated by centrifugation. The microspheres may be stored in hexane.

Dispersion of Drug-Loaded Albumin Microspheres in Propellant

Albumin microspheres dispersed in hexane are centrifuged and washed with Freon 11. The microspheres are then dispersed in 6 g of Freon 11 and placed in pressurizable aerosol device. Fourteen grams of Freon 12 is filled into the above device and mixed well after the devise is crimped. The dispersion of the microspheres containing procaterol hydrochloride in the propellant Freon 11 and Freon 12 is ready for metered-dose inhalation use.

EXAMPLE 2

An aqueous solution (1 ml) containing 20 mg of procaterol hydrochloride, 10 mg of ascorbic acid and 170 ml of bovine serum albumin is mixed with 100 ml cottonseed oil containing 0.2 ml of α-tocopherol and the mixture is sonicated for 1.5 minutes at 50°C to prepare an emulsion. The microspheres are then prepared as described in the above example.

CLAIMS

1. A controlled-release pharmaceutical formulation for use in an inhalation aerosol comprising a pharmaceutically active agent and albumin, optionally together with oil and aqueous soluble stabilizers, in the form of microspheres.

2. A formulation of Claim 1 wherein the pharmaceutically active agent is procaterol hydrochloride.

3. A formulation of Claim 2 wherein the stabilizers are 1) ascorbic acid or 2) ascorbic acid and α-tocopherol.

4. A pharmaceutical composition for delivery of a pharmaceutically active agent by inhalation aerosol comprising the microspheres of Claim 1 in pressurized air or propellant.

5. A composition of Claim 3 wherein the agent is a high-potency agent.

6. A composition of Claim 5 wherein the agent is a bronchodilating agent.

7. A composition of Claim 6 wherein the bronchodilating agent is procaterol hydrochloride.

8. A composition of Claim 7 where the propellant is a chlorofluorohydrocarbon.

9. A method of treatment by inhalation aerosol using the formulation of Claim 1.

10. A process for preparing a pharmaceutical formulation of Claim 1 comprising 1) encapsulating a high potency pharmaceutically active agent by a)preparing an aqueous suspension of 2 to 200 mg/ml of the agent and 18 to 1800 mg/ml serum albumin; b)mixing the suspension in 18 to 1800 mg/ml oil; c) emulsifying the mixture by sonification for 0.5 to 3 min.; d)heating the emulsion to a temperature of from 80° to 140°C for from 2 to 60 min.; and 2) dispersing the microspheres resulting from d) in a propellant.

11. A process of Claim 10 wherein a) the aqueous suspension is 1 ml of water containing 20 mg of procaterol hydrochloride and 180 mg of bovine serum albumin; b) the suspension is mixed in 100ml of cottonseed oil; c) the mixture is emulsified by 1.5 min. of sonication; d) the emulsion is heated for 30 min. at 110°C and then the resulting microspheres are dispersed in 6 g of Freon 11 and then further charged with 14 g of Freon 12.

12. A process of Claim 11 wherein the aqueous suspension contains 10 mg of ascorbic acid and the cottonseed oil contains 0.2 ml of α-tocopherol.

13. A microsphere-in-propellant which is a dispersion suitable for providing controlled-release by inhalation aerosol comprising a formulation of Claim 1.

14. The microsphere-in-propellant which is a dispersion suitable for providing an inhalation aerosol of the formulation of Claim 3.

15. The microsphere-in-propellant which is a dispersion suitable for providing an inhalation aerosol of the formulation of Claim 3 wherein the albumin is bovine albumin.

16. An inhalation device for delivery by inhalation aerosol having a controlled-release formulation of Claim 1 comprising a pharmaceutically active agent encapsulated in albumin optionally stabilized.

17. The device of Claim 16 wherein the agent is procaterol hydrochloride.

18. A device of Claim 16 wherein the device is a pressurized dose-aerosol containing a self-propelling composition comprising the formulation and a propellant.

19. The device of Claim 16 wherein the formulation is microspheres having procaterol hydrochloride encapsulated in albumin stabilized by ascorbic acid and α-tocopherol.

GLAX B05 1993-213779/26 =RU 2129424-C1

Surfactant free aerosol formulation for treatment of e.g. asthma - uses ozone-friendly fluorocarbon or hydrogen contg. chloro-fluorocarbon propellant

GLAXO GROUP LTD 1992.02.06 1992GB-002522 (1991.12.12 1991GB-026378)

(1999.04.27) *WO 9311743-A1 *A61K 9/12, 31/56*

1992.12.04 1994RU-030722 1992.12.04 1992WO-EP02808 Based on WO9311743-A (Eng)

Addnl.Data: 1991.12.12 1991GB-026405

1993-213780/26 1993-213781/26

Formulation comprises a particulate medicament (I) e.g. salmeterol, salbutamol, fluticasone propionate, becolomethasone dipropionate and a fluorocarbon or hydrogen-contg chlorofluorocarbon propellant.

Also claimed are the prepn of the surface-modified medicament and a canister for delivering metered doses of the aerosol formulation.

Pref., (I) is salmeterol xinafoate (Ia); salbutamol sulphate; fluticascone propionate; beclomethasone dipropionate; or a combination of salmeterol xinafoate and fluticasone propionate; or salbutamol and beclomethasone dipropionate. The propellant is pref. 1,1,1,2-tetrafluoroethane (II). (I) is present in an amt. of 0.005-10% wt. based on the total wt. of the formulation e.g. a salbutamol salt and 1,1,1,2-tetrafluoroethane in a ratio of 0.05:18 by wt. Surface-modified (I) are prepd. by admixture of particulate (I) with a non-polar, non-solvent liq. followed by removal of the lid.

USE/ADVANTAGE - The aerosol formulations are 'ozone friendly' using H-contg. chlorofluorocarbons as propellants and having no requirement for added surfactants or solvents for stabilising the constituent medicament(s). (I) can be used separately or in combination and may be e.g. analgesics, antiallergics, antiinfectives, antihistamines, anti-inflammatories, bronchodilators, diueretics, hormones, or therapeutic proteins and peptides. Admin. is by inhalation. Dosage of (I) is 50-2000 micro-g per day.

GLAX B01 1993-272545/34 =RU 2120285-C1

Aerosol formulations contg. beclomethasone di:propionate mono:hydrate - have specified water content for prolonged stability

GLAXO GROUP LTD 1992.02.06 1992GB-002519

*P34 (1998.10.20) *WO 9315741-A1 A61K 31/56, 9/12, A61L 9/04*

1993.02.02 1994RU-040361

Compsn. comprises (by wt): a) beclomethasone dipropionate monohydrate (pref. 0.005-10%) of particle size substantially less than 20 microns alone or in combination with salbutamol or salmeterol xinafoate; (b) at least 0.015% pref. 0.026-0.08% of the formulation of water in addition to the water of crystallisation assoc. with said monohydrate and c) a fluorocarbon or hydrogen-contg. chlorofluorocarbon propellant (pref. 1,1,1,2,3,3,3-hepafluoro -n-propane or 1,1,1,2-tetrafluoroethane).

USE/ADVANTAGE - The formulations are stable and the particle size does not increase on staorage due to solvates formulating so that the medicament particles do not become too large to penetrate the lungs. Daily doses of beclomethasone dipropionate are in the range (100-2000mcg given by filled canisters and metered dose inhalers, 1-4 puffs, 1-8 times per day